

III. REMARKS

Claims 1, 3, 5-7, 11, 18, 28, and 29 are pending. New Claims 31-47 are drawn to methods of use, and are addressed separately from the currently proposed amendments.

Support for the amendments to Claims 1, 3, 6, 7, 11, and 18 can be found on pages 11 and 17. Support for new Claims 31-40 can be found on pgs. 45-46. Support for new Claims 41-47 can be found on pg. 46-47.

1. Office has rejected Claims 1, 3, 6, 7, 11, and 18 under 35 U.S.C. 101 as embracing “naturally occurring, non-isolated nucleic acid compositions in which the hand of man is not evident.”

Applicants believe that the rejection under 35 U.S.C. 101 is rendered moot in light of the proposed amendments to the claims. Proposed amendments to Claims 1, 3, 6, 7, 11 and 18 recite an “isolated nucleic acid.”

2. Office has rejected Claims 3, 5-7, 11, and 18 under 35 U.S.C. 112 2nd paragraph as being indefinite as “it is unclear what is intended by ‘between 90% to 100%.’”

Applicants believe that the rejection under 35 U.S.C. 112 is made moot in light of the proposed amendments to the claims. As suggested by the Examiner, proposed amendment to Claim 3 deletes the word ‘between.’ Claims 5-7, 11, and 18 are dependent upon Claim 3.

3. Office has rejected Claims 1, 3, 5-7, 11, 18, 28 and 29 as containing subject matter not properly described in the specification.

Applicants believe that the rejection under 35 U.S.C. 112 is rendered moot in light of the proposed amendment to the claims. The proposed amendment to Claim 1 replaces ‘having’ with ‘consisting of.’

4. Office has rejected Claim 3 and dependents therefrom as indefinite such that their scope cannot be determined.

The Office asserts on page 5, lines 10-11 that “a sequence 90-100% identical to SEQ ID NO: 58” is indefinite. As explained on page 13, lines 15 to 20 of the specification,

When the individual units (e.g., nucleotides or amino acids) of the two molecules are schematically positioned to exhibit the highest number of units in the same position over a specific region, a percentage identity of the units identical over the total number of units in the region is determined. Numerous algorithmic and computerized means for determining a percentage identity are known in the art

One of skill in the art would appreciate that “a sequence 90-100% identical to SEQ ID NO: 58” would embrace a finite number of nucleic acid sequences and would at once be able to envision most if not all of such sequences upon reading the applicant’s disclosure.

The Office states that, “one of skill in the art could not conclude that Applicant was in possession of [the species] at the time the invention was filed.” To the extent that the ‘species’ the Office refers to are full length cDNAs, applicants believe that the proposed amendments render this rejection moot. To the extent that the ‘species’ the Office refers to are embraced by the claims, including the proposed amendments, applicants respectfully note that as the invention as claimed, as evidenced on page 71, lines 16 through page 72, line 9 of the specification, was actually reduced to practice. As such, the applicants clearly had possession of the invention at the time of the present application was filed.

5. Claims embracing Nucleic Acid Sequences

Office has rejected Claims 1, 3, 5-7, 11, 18, and 28 as lacking utility under 35 U.S.C. 101 and non-enabled 35 U.S.C. 112. Claims 1, 3, 5-7, 11, 18, and 28, including the currently proposed amendments, embrace isolated nucleic acid sequences.

A. Utility of Nucleic Acid Sequence Claims

According to MPEP 2107.01, III A., “[a]s a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility

requirement of Section 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.” In *re Langer*, 183 USPQ 288 at 297. Applicants have disclosed 27 non-limiting, illustrative utilities for the present invention on pages 3-8 of the specification. Exemplary categories of utility include utility in generating diagnostic reagents (pg. 3), utility identifying targets for small molecule drug development (pg. 5), utility in the direct generation of therapeutics (pg. 7), and facilitation in cloning the complete gene (pg. 8). As such, the present invention should be considered useful in the absence of “a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.” In *re Langer*, at 297. The Office has not provided any reason for one skilled in the art to question applicants’ statement of utility of the claimed sequences. As such, applicants respectfully request withdrawal of the 35 U.S.C. 101 rejection.

B. Enablement of Nucleic Acid Sequence Claims

According to MPEP 2164.04, “the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention.” In *re Wright*, 27 USPQ2d 1510 at 1513 (Fed. Cir. 1993). According to *United States v. Teletronics, Inc.*, “[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.” *United States v. Teletronics, Inc.*, 8 USPQ2d 1217 at 1223 (Fed. Cir. 1988).

The Office states on page 10 of the Office Action dated 22 July 2003 that, “[e]nablement of the use of the claimed polynucleotides as diagnostics for OA, for drug development, or for therapy, depends on the establishment of a relationship between OA and the polynucleotides.” With respect to the claims embracing the nucleic acid sequences, applicants note that enablement under 35 U.S.C. 112 only requires that “the specification describe how to make and how to use the present invention.” MPEP 2164. Applicants note that to make and use the nucleic acid sequences embraced by the present invention, it is not necessary to know the relationship between OA and the

polynucleotides, rather it is only necessary that one of ordinary skill in the art would be able to isolate the sequences of the present invention and use them for any one of the utilities discussed on pages 16-26 of the specification. With respect to the newly proposed claims regarding methods of using such nucleic acid sequences, applicants briefly note that such methods are taught on pages 26-71 of the specification. A full discussion of the utility and enablement of methods of the present invention is discussed below in Section 6.

Office states that, "it is unclear what is meant by "preferentially observed." "Preferentially observed" means the ability of a first test compound to preferentially bind to a receptor or other biologically active portion of a second compound as compared to a known compound. Support for this definition can be found on pages 46, 47, 48, and 71 of the specification.

The Office states on page 10 of the Office Action dated 22 July 2003 that, "the specification fails to provide adequate information to allow one of ordinary skill in the art to assess critical variables related to the preparation of the libraries and the natural variability in expression among individuals, and the specification provides no guidance with regard to what is the threshold between normal and disease-related expression levels in of any gene in OA." Applicants note that to make and use the nucleic acid sequences of the present invention, for example SEQ ID NO. 58, one of ordinary skill in the art does not need to "assess critical variables related to the preparation of the libraries." Additionally, applicants assert that to make and use the nucleic acid sequences of the present invention, for example SEQ ID NO. 58, one of ordinary skill in the art does not need to know the "threshold between normal and disease-related expression levels in of any gene in OA."

As such, applicants respectfully request withdrawal of the 35 U.S.C. 112 rejection.

6. Claims embracing Methods of using Nucleic Acid Sequences to Identify Osteoarthritis Modulators.

Applicants believe that the proposed amendments of new claims embracing methods of identifying osteoarthritis modulators are useful and satisfy both the written description requirement of 35 U.S.C. 112 and the enablement requirement of 35 U.S.C. 112. Applicants recognize that these proposed claims are new and have not yet been examined by the Office. In order to advance the status of the present application, applicants will address the utility and enablement of the proposed method claims.

According to MPEP 2164.01, "[t]he standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261 at 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable?" Fannon, an article cited by the office in the action dated 22 July 2003, states that, "[w]ork is needed to quantify how much variation in gene expression may be considered 'healthy' or 'normal' and at what point the expression pattern shifts to the 'disease' profile." (Col. 297, lines 7-10). Applicants note that the preceding sentence acknowledges that, "Expression patterns vary among individuals,... and in response to environmental stimuli." (Col. 297, lines 5-7). Applicants note that a perfect correlation between expression and disease profile is not a requirement for patentability, and moreover, is only achievable in theory. As the case study on page 297 of Fannon demonstrates, experimentation with bioinformatic factors to correlate expression with disease profile is routine. With respect to the present invention, one of ordinary skill in the art would appreciate the correlation of up or down regulated expression to the probability of developing OA. As stated on page 64, lines 18 through 28 of the present application,

For example, the effectiveness of an agent determined by a screening assay as described herein to increase gene expression, protein levels, or upregulate protein activity, can be monitored in clinical trials of subjects exhibiting decreased gene expression, protein levels, or downregulated protein activity. Alternatively, the effectiveness of an agent determined by a screening assay to decrease gene expression, protein levels, or downregulate protein activity, can be monitored in clinical trials of subjects exhibiting increased gene expression, protein levels, or upregulated protein activity. In such clinical trials, the expression or activity of the specified gene and, preferably, other genes that have been implicated in, for

example, a proliferative disorder can be used as a "read out" or markers of the phenotype of a particular cell.

At the time of filing the present application, a number of well-known, computer-implemented processes exist for correlate sequence identity to disease. As described on pages 14-15 of the specification,

A variety of computerized means for correlating expression with disease include five implementations of BLAST, three designed for nucleotide sequences queries (BLASTN, BLASTX, and TBLASTX) and two designed for protein sequence queries (BLASTP and TBLASTN), FASTA, HMMer, MEME and PSI-BLAST, ORF, PROSITE, Teiresias, SPASM, and RIGOR.

On page 9, the Office states that, "it is unclear how the comparison was made, how many donors contributed to each library, if the contributions were equal, or if the synovial tissue was represented in each library...." As stated by Applicants on page 71, lines 19 through 23:

Three EST libraries of OA cartilage and synovium from 6 different donors (five cartilage donors and one synovium donor) were compared to two EST libraries representing cartilage and synovium from 5 donors (four cartilage donors and one synovium donor) without OA to identify those ESTs which are representative of genes upregulated as a result of OA. (emphasis added)

Applicants respectfully note that the number of donors contributing to each library has been clearly stated, and further, that it is clear that synovial tissue was represented in each library.

As proposed amendments of new claims embracing methods of using nucleic acid sequences to identify osteoarthritis modulators have utility as required by 35 U.S.C. 101 and satisfy both the written description requirement of 35 U.S.C. 112 and the enablement requirement of 35 U.S.C. 112, applicants respectfully request entry and allowance of the new claims included in the proposed amendments.

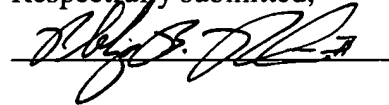
Appl. No. 09/765,231
Amendment Dated 8 December 2003
Reply to Office Action of 22 July 2003

In view of the foregoing, applicants believe that the present application is in condition for allowance.

If a telephonic interview with Applicant's representative would aid in the prosecution of this application, the Examiner is cordially invited to contact Applicant's representative at the below listed number.

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Respectfully submitted,

A handwritten signature in black ink, appearing to read "Philip B. Polster II", written over a horizontal line.

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